ORIGINAL ARTICLE

A Significant Association in Paediatric Emergency Department, Cerebral Sinovenous Thrombosis and Ulcerative Colitis: Review of Literature

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ABSTRACT

Objective: *To discuss cerebral sinovenous thrombosis (CSVT), an important mortality and morbidity factor, developing in the progression of ulcerative colitis (UC) in childhood age, in the light of the literature.*

Methods: *A search of PubMed and Google Scholar database was conducted on April 2014. This study retrospectively investigates the cases diagnosed with UC with complication of CSVT below 18 years of age between years 1971 and 2014. The cases were analysed with respect to age, gender, disease duration and treatment, potential risk factors, clinical findings, location of thrombosis, thrombolytic therapeutical applications, and clinical progressions.*

Results: *Twenty-four paediatric patients aged 5 and 18 years were included in the study. Cerebral sinovenous thrombosis had developed during active disease period in 23 (95.8%) patients. The most common complaints were headache (79.1%) and emesis (29.1%). The most frequently detected risk factors for CSVT were anaemia (58.3%) and thrombocytosis (45.8%). Inherited thrombotic disorders were encountered in 10 (41.6%) of the cases. The most common location sites for CSVT were the transverse (33.3%) and the sigmoid (33.3%) sinuses. It had been discovered that 19 (79.2%) of the cases were healed completely without a sequelae, whereas neurological sequelae remained in three (12.5%) of the cases and two (8.3%) of the cases died.*

Conclusion: *In the presence of a prior diagnosis of UC and emergency presentation with emesis, headache, mood changes and particularly seizure, the presence of CSVT should certainly be considered.*

Keywords: Cerebral sinovenous thrombosis, child, emergency department, ulcerative colitis.

INTRODUCTION

Cerebral sinovenous thrombosis (CSVT) developing secondary to obstruction in the veins functional in venous drainage of the brain is an important cause of morbidity and mortality that is quite rarely observed in the childhood age. Its incidence is 0.25–0.67/100 000 (1, 2). Of the CSVT cases in this age group, 5%–12% showed fatal progression while permanent neurological sequelae developed in 61%–74% of the cases (2). The potential risk factors associated with CSVT in childhood include prematurity, trauma, chronic inflammatory disorders, surgical operation, cardiac diseases, traumatic venous sinus damage, nephrotic syndrome, malignancy, head and neck infections, and dehydration (2, 3). The risk for cerebrovascular complication in inflammatory bowel disease (IBD), being one of the risk factors of CSVT, is 1.3%–3.3% (3). The development of CSVT demonstrates a three- to fourfold elevation in IBD (4). Its pathogenesis is considered to be associated with increased inflammatory response, genetic predisposition, loss of procoagulant factors through gastrointestinal system, temporary abnormalities in clotting system, increased levels of factor V and VIII besides

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the decreased levels of protein S and anti-thrombin III during the disease's progression (5).

This study aimed to a description and discuss the risk factors, clinical and laboratory findings, treatment, and the prognosis of CSVT which is an important mortality factor in the progression of ulcerative colitis (UC) during childhood age, in the light of the literature review.

SUBJECTS AND METHODS

Review method

PubMed and Google Scholar search databases were screened in April 2014. This screening was done using the keywords 'cerebral venous thrombosis in childhood, thrombosis and/or thromboembolism and/or stroke, colitis, ulcerative colitis and/or inflammatory bowel diseases, infant or child or adolescent or paediatric'. All of these keywords were screened in the databases without a language limitation and all of the potentially related articles were evaluated.

The study was done to analyse the cases of patients below 18 years of age diagnosed with UC accompanied with developing CSVT from 1971 to 2014. The cases were analysed with respect to their age, gender, disease progression and treatment, potential risk factors for thrombosis, radiological findings, accompanying symptoms and findings, thrombolytic treatment applications, and clinical progressions.

RESULTS

Demographic findings

The study included 24 child cases followed up with the diagnosis of UC accompanied with developing CSVT (Table 1). The mean ages of the cases were 13.0 ± 3.7 (ranging 5–18) years. The ratio of females to males was 1. The incidence ages of CSVT in the female and the male children were 13.3 ± 3.9 and 12.7 ± 3.8 years. Lloyd *et al* (6) reported the youngest case who was a 5-year-old female patient. Most of the cases (18/24, 75%) were in the adolescent age group (> 10–18 years). The childhood age group (≤ 10 years) included six (25%) cases (Table 1). The age at diagnosis and time to the development of thrombosis in four cases were not reported. The mean age at diagnoses of the reported 20 cases was 11.7 ± 2.7 years, and median value of the time to the development of CSVT after the diagnosis of UC was 10.5 months (range, 0.5–66.0 months) (Table 1). The earliest time to the development of thrombosis during the disease progression was 2 weeks as reported by Barclay *et al* (7). The longest time to the development of CSVT after UC was 66 months (5). Thrombosis developed during the active stage of the disease in 23 (95.8%) of the cases, whereas the disease was not in the active stage in only one case. Of the cases, 4 (16.6%), 3 (12.5%) and 15 (62.5%) cases were receiving only 5-aminosalicylic acid, only steroid and combined therapy, respectively. The treatment protocol of two of the cases had not been reported (Table 1).

Clinical findings

All the patients were symptomatic (Table 1). The analyses of the baseline symptoms revealed the most common application rationale such as headache (19 cases, 79.1%) and emesis (7 cases, 29.1%). The accompanying clinical findings are summarized in Table 2.

Prothrombotic risk factors

The most frequently observed risk for CSVT in the patients with UC was anaemia (14 patients, 58.3%) and thrombocytosis (11 patients, 45.8%). Thrombosis and anaemia were the only detectable risk factors for CSVT in three (12.5%) and two (8.3%) patients, respectively. Companionship of anaemia and thrombocytosis was present in eight (33.3%) of the cases. The incidence of the risk factor for anaemia in the childhood age group (≤ 10 years) was 33.3% (2/6) whereas that was 61.1% (11/18) in the adolescent age group. The incidence of the risk factor for thrombocytosis in the childhood age group was 33.3% (2/6), whereas it was 50% (9/18) in the adolescent age group. Among the risk factors, inherited thrombotic disorders were detected in 10 (41.6%) of the cases. The most frequently observed inherited thrombotic disorders were the mutation of methylene-tetra-hydro-folate reductase (three patients, 12.5%) and anti-thrombin III deficiency (three patients, 12.5%), respectively. The incidence of inherited thrombotic disorders in the childhood age group was 50% (3/6), whereas it was 38.8% (7/18) in adolescent age group. The risk factors of thromboembolism reported in the cases with UC are shown in Table 3.

Radiological findings

The number of cases in whom CSVT was encountered in the multiple locations was 12 (50.0%). In the cases with the expressed location sites, CSVT was most commonly located in transverse sinus (eight patients, 33.3%), sigmoid sinus (eight patients, 33.3%) and superior sagittal sinus (seven patients, 29.1%), respectively (Fig. 1).

Table 1: Paediatric case reports from patients with UC accompanied with CVST

Author	Age	Sex	UC diagnosis (month)	Treatment	Symptoms	Localization of thromboemboli	Risk factors	Anticoagulation	Outcome
Lloyd-Still *et al* (6)	5	F	UR	Steroids, salicylazosulfapyridine	Pitozis, headache, loss of vision	CVST	Anaemia	UR	CR
Kao *et al* (14)	7	F	4	5-ASA	Headache, aphasia	TS, SS, IJV	Anticardiolipin Ab	LMWH	Mild right pronator drift
Lloyd-Still *et al* (6)	7	M	UR	Steroids, salicylazosulfapyridine	Encephalopathy	Possible SSS	Anaemia, thrombocytosis	UR	CR
Kutluk *et al* (15)	9	M	24	Steroids, 5-ASA, AZA	Pitozis, papilledema, headache	TS, SS	Anaemia, thrombocytosis, MTHFR gene mutation	Heparin, LMWH	CR
Robison *et al* (16)	10	M	36	Steroids	Headache, vomiting	TS, SS, GV, ISS	FVL mutation, MTHFR gene mutation	LMWH	CR
Calderon *et al* (8)	10	F	4,5	Salicylazosulfapyridine, steroids	Drowsiness, dizziness, headache, vomiting, asimetrik, pupil nistagmus, hemiparesis	CVST	AT III deficiency factor VIII	UR	Died 15 days later
Mahmoud Reza A *et al* (4)	11	M	3	Steroids, 5-ASA	Papilledema, orbital pain, headache	SSS	Anaemia, thrombocytosis	Heparin, warfarin	CR
Paradis *et al* (12)	12	F	1	Steroids, salicylazosulfapyridine	Headache, vomiting, facial weakness, right hand and foot numbness	SSS	Anaemia, thrombocytosis	UR	CR
Schneiderman *et al* (13)	12	F	12	Salicylazosulfapyridine, steroids	Headache, seizures, hemianopia, diplopia, vomiting	Short circumferential veins	Elevated factor VIII	No	Died 2 days later
Keene *et al* (11)	12	M	1	Steroids	Orbital pain, papilledema	CVST, SSS	Anaemia, thrombocytosis, AT III deficiency	No	CR
Shaikh *et al* (49)	PT		2	Steroids, 5-ASA	Headache, nausea confused, altered mental status and bilateral lower extremity weakness	GV, ISS	Anaemia	Heparin, LMWH	CR
Barclay *et al* (7)	13	M	0.5	Steroids, salicylazosulfapyridine	Sleep, headaches, vomits, ataxia, hemiplegia	TS, ISS.	Anaemia, thrombocytosis, immobile	Aspirin.	Hemiplegia
Kao *et al* (14)	13	F	18	–	Seizures	SSS, TS, SS, CV, IJV	Homocystinaemia, G20210A	LMWH	CR
Al Tahan *et al* (50)	14	F	5	Steroids, 5-ASA	Headache, seizures	SSS	Anaemia, Pro-S deficiency	Heparin, warfarin	CR
Kao *et al* (14)	14	F	36	–	Hemiparesis	SS, CV	No	Heparin, warfarin	Left hemiparesis
Markowitz *et al* (17)	14	M	9	Steroids, 5-ASA	Headache, hemiparesis, aphasia	LS, SS	Anaemia, thrombocytosis	Aspirin	CR
Ben Sassi *et al* (31)	15	F	UR	5-ASA	Headache, vomiting, seizures	LS	Thrombocytosis	Heparin, warfarin	CR
Houissa *et al* (9)	16	F	48	5-ASA	Headache, confusion	CSVT	Thrombocytosis	LMWH	CR

(*cont'd overleaf*)

Table 1 (*cont'd*)

Author	Age	Sex	UC diagnosis (month)	Treatment	Symptoms	Localization of thromboemboli	Risk factors	Anticoagulation	Outcome
Our case	17	F	18	5-ASA	Headache, aphasia	TS, SS, İJV	Anaemia, thrombocytosis, MTHFR gene mutation	LMWH	CR
Macri *et al* (51)	17	F	1	Steroids, 5-ASA	Headache, seizures, aphasia, hemiparesis	SSS, CV	Anaemia, AT III deficiency, OC	LMWH	CR
Diakou *et al* (52)	17	M	18	Steroids, AZA	Headache	TS, SS	Pro-S deficiency	Heparin, warfarin	CR
Cognat *et al* (53)	18	M	60	Steroids, 5-ASA	Headache. hemianopia	LS	Anaemia	Heparin, warfarin	CR
Thorsteinsson *et al* (5)	18	M	66	Steroids, AZA, 5-ASA	Headache, vomiting	TS	Anaemia, peritonsillitis incision	Heparin, warfarin, fondaparinux	CR
Rousseau *et al* (10)	18	M	UR	Steroids	Hemiplegia, hemiparesthesia	CVST	Thrombocytosis	UR	CR

M = male; F = female; UR = unreported; AZA = azathioprine; 5-ASA = 5-aminosalicylic acid; CVST = cerebral venous sinus thrombosis; SSS = superior sagittal sinus; LS = lateral sinus; TS = transverse sinus; SS = sigmoid sinus; ISS = inferior saggital sinus; IJV = internal jugular vein; CV = cortical veins; GV = Venous of Galen; Pro-S = protein S; AT III = anti-thrombin III; MTHFR = methylene-tetra-hydro-folate-reductase; FVLm = heterozygous for factor V Leiden mutation; OC = oral contraceptives; G20210A = prothrombin gene G20210A mutation; LMWH = low molecular weight heparin; CR = complete recovery.

Table 2: Clinical findings in UC patients with CVST

Clinical presentations	n (%)
Headache	19 (79.1)
Emesis	7 (29.1)
Hemiparesis	6 (25.0)
Seizures	5 (20.8)
Aphasia	4 (16.6)
Papilledema	3 (12.5)
Hemiplegia	2 (8.3)
Pitozis	2 (8.3)
Hemianopsia	2 (8,3)
Orbital pain	2 (8.3)
Confusion	2 (8.3)
Diplopia	1 (4.1)
Facial weakness	1 (4.1)
Ataxia	1 (4.1)
Loss of vision	1 (4.1)
Droop	1 (4.1)
Dizziness	1 (4.1)
Drowsiness	1 (4.1)
Nistagmus	1 (4.1)
Numbness	1 (4.1)
Nausea	1 (4.1)
Encephalopathy	1 (4.1)

UC = ulcerative colitis; CVST = cerebral venous sinus thrombosis.

Table 3: Risk factors for thrombosis in patients with UC

Factors	n (%)
Anaemia	14 (58.3)
Thrombocytosis	11 (45.8)
Antithrombin III deficiency	3 (12.5)
MTHFR mutation	3 (12.5)
Protein S deficiency	2 (8,3)
Elevated FVIII	2 (8,3)
Factor V Leiden mutation	1 (4.1)
Anticardiolipin antibody	1 (4.1)
Prothrombin gene mutation (G20210A)	1 (4.1)
Homocystinaemia	1 (4.1)
Immobilite	1 (4.1)
Peritonsilitis	1 (4.1)
Oral contraceptive use	1 (4.1)

UC = ulcerative colitis; MTHFR = methylene-tetra-hydro-folate-reductase.

Table 4: Therapy in children with TE in UC

Treatment protocol	n (%)
Only LMWH	6 (25.0)
Heparin+warfarin	6 (25.0)
Heparin+ LMWH	2 (8.3)
Heparin+warfarin +anti-factor X	1 (4.2)
Only aspirin	2 (8.3)
Unreported	5 (20.9)
Untreated	2 (8.3)
Total	24 (100.0)

TE = thromboembolism ; UC = ulcerative colitis; LMWH = low molecular weight heparin.

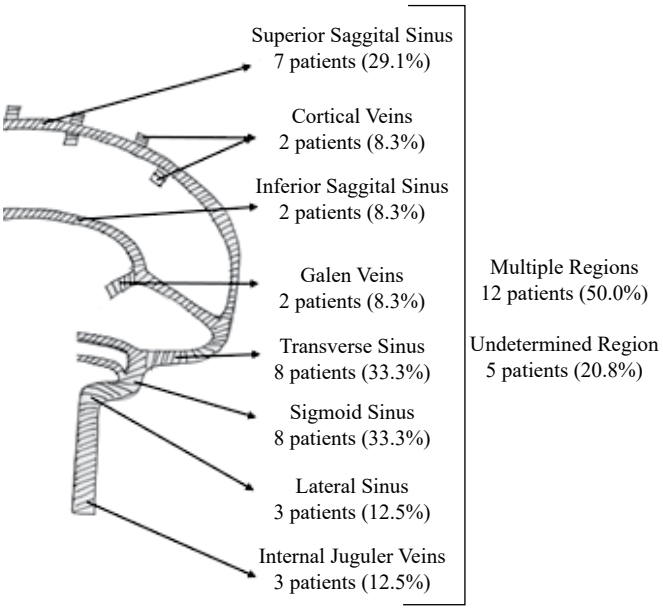

Fig. 1: Sites of cerebral venous sinus thrombosis in patients with ulcerative colitis.

The location site of the thrombus was reported as only CSVT in five (20.8%) of the patients (6, 8–11). The most common location in the adolescent age group was the transverse sinus, whereas the most common location in the childhood age group was sagittal sinus.

Treatment and outcome

Heparin, low molecular weight heparin (LMWH), warfarin, aspirin, and anti-factor Xa were administered in, respectively, 9 (47.3%), 8 (42.1%), 7 (36.8%), 2 (10.5%), and 1 (5.2%) of the 19 cases whose treatment protocols were expressed. Warfarin, LMWH and anti-factor Xa were administered after the medication with heparin in seven (36.8%), two (10.5%) and one (5.2%) of the cases, respectively (Tables 1 and 4).

During the follow-up period under heparin therapy, one patient was complicated with heparin-induced thrombocytopenia type II but recovered completely after exchanging the anticoagulant to fondaparinux (5). The treatment protocols of five cases were not expressed (6, 8, 10, 12), while it was expressed that anticoagulant therapy was not administered in two cases because of the risk for bleeding (11, 13) (Tables 1 and 4). Only heparin or LMWH medication was preferred in the three patients whose treatment protocols were administered in the childhood age group (14–16) (Table 1). Of the patients who were treated heparin or LMWH, 86.6% (13/15) were healed completely while 13.3 (2/15) were recovered partially (14). Of the patients who received aspirin treatment, one patient remained hemiplegic (7), whereas the other patient was recovered completely (17).

It has been reported for the 24 cases followed with CSVT that 19 (79.1%) of them cases were healed completely, whereas neurological sequelae (mild right pronator drift (14), hemiplegia (7), hemiparesis (14)) remained in 3 (12.5%) cases while 2 (8.3%) cases became exitus (8, 13). Grand Mal epilepsy was reported as the cause of death (13), while the development of sepsis after meningitis due to *Staphylococcus aureus* and *Enterobacter cloacae* was the cause of death in the other exitus patient (8). Anticoagulant therapy was not given in one of the exitus cases (13), while the treatment protocol was not reported in the other exitus case (8). Of the two cases who were not given anticoagulant therapy because of bleeding risk, one died (13) whereas the other cases recovered completely (11).

Our case

The 17-year-old female patient attended the applied Paediatric Emergency Department with complaints of meaningless speech and extreme difficulty in expressing herself, understanding words and naming objects that continued for the recent 2 days, headache, bloody mucus in the stool and fatigue that existed for the recent 10 days. We were informed that our patient was diagnosed 1.5 years ago, and she regularly used mesalazine and had two attacks of UC flares, the last one being 4 months ago, in her medical history. The physical examination of the patient revealed no abnormal finding except Wernicke's aphasia, headache and paleness. The laboratory test results are as follows: white blood cell count: 13 360/mm^3, haemoglobin (Hb): 6.3 g/dL, haematocrit: 24%, mean corpuscular volume: 57.1 fL, red blood cell distribution width: 19%, thrombocyte: 724 000/mm^3, Fe: 9.7 µg/dL, total iron binding capacity: 241.9 µg/dL, ferritin: 10.8 ng/ml, sedimentation: 30 mm/hour, C-reactive protein: 31 mg/dL, prothrombin time: 14.1 seconds, activated partial thromboplastin time: 27.3, and prothrombin time-international normalized ratio: 1.17.

The other blood and urine findings were normal. Brain magnetic resonance imaging (MRI), diffusion MRI and magnetic resonance venography encountered thrombosis of left internal jugular vein, sigmoid sinus and transverse sinus and cytotoxic oedema with diffusion limitation in the left temporal lobe (Figs. 2–4). The LMWH and treatment of intravenous iron were initiated.

Erythrocyte transfusion was done. The tests for thrombosis demonstrated only positive heterozygous

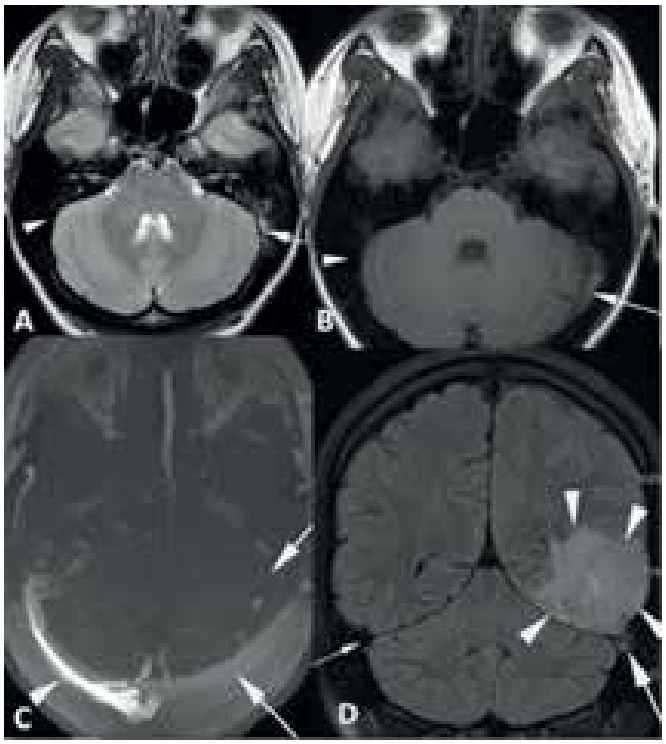

Fig. 2: Left sigmoid sinus thrombosis in T2 (A) and T1 (B) weighted imagings. Normal signal void patterns of right sigmoid sinus in T2 (A) and T1 (B) weighted imagings (arrowhead). The interruption of left transverse and sigmoid sinus flows in time-of-flight MR angiography (C) (arrow). The normal right transverse and sigmoid sinus flows in time-of-flight MR angiography (arrowhead). Left sigmoid sinus thrombosis (thick arrow), hyperintensity in temporal lobe cortical, subcortical and deep white matter in the areas due to venous infarction (arrowhead), and normal right sigmoid sinus flows (thin arrow) in fluid-attenuated inversion recovery sequence (D).

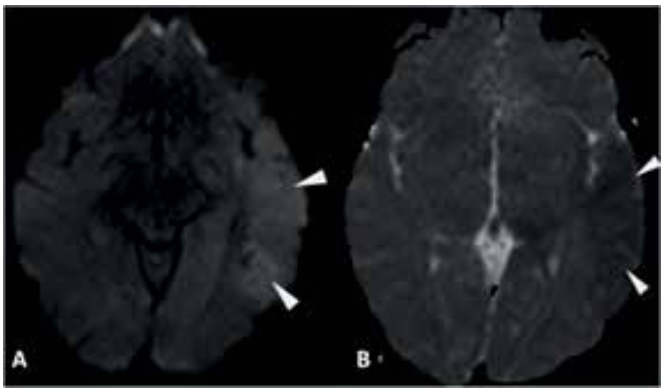

Fig. 3: (A, B) The decrease of diffusion because of cytotoxic oedema in diffusion weighted imaging (arrowheads).

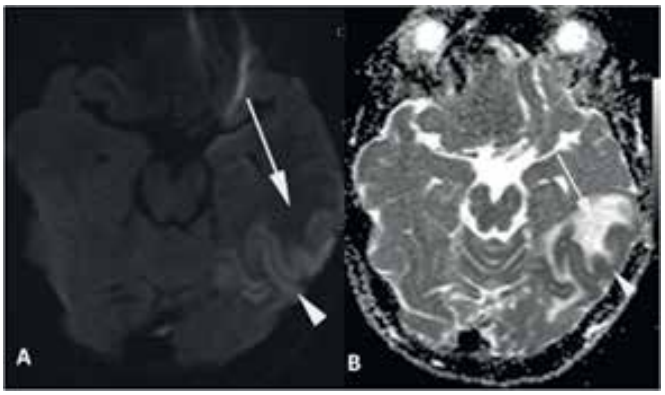

Fig. 4: Five days after LMWH treatment, the improving of diffusion because of cytotoxic oedema in diffusion weighted imaging images (A, B) (arrowheads) and the appearance of increased diffusion areas secondary to vasogenic oedema (arrow).

MTHFR mutation. The patient whose clinical and radiological findings improved due to treatment of LMWH was discharged to be followed up in the polyclinic.

DISCUSSION

The CSVT that may be observed in the progression of UC as one of the potential extraintestinal symptoms is an important mortality and morbidity factor (5, 18). Patterson *et al* (19) reported the first thromboembolic complication due to IBD in childhood age. The risk for venous thromboembolism (VTE) in the case of IBD ranged between 1% and 8% in all age groups whereas that risk ranged between 39% and 41% in the cases of post-mortem autopsy (20).

Besides, the rate of vascular complications that led to thromboembolic events due to IBD also ranges between 1.3% and 3.3% in the paediatric age group (3). Venous thromboembolism occurred average 1.75 years (1–8 years) after the onset of IBD (3). This situation occurred frequently during the progression of UC in the adulthood age group; however, it is quite rare and appears as case presentations. Venous thromboembolism, which also involved CSVT in the child patients with UC, was observed mostly in the early childhood period (21). In the cohort study conducted by Nguyen ve Sam (21), it has been reported that in the childhood age group VTE significantly increased (relative risk (RR) 13.7, 95% confidence interval (CI) 4.1, 45.3, $p < 0.001$) in children with UC in the age range 0–10 years comparatively with non-IBD children diagnosed with VTE and found to be 0.44%. In the same study, it was reported that the risk for VTE in the children with UC showed significantly no increased risk (RR 1.3, 95% CI 0.7, 2.2, $p < 0.3$) when compared with the non-IBD children diagnosed with UC in age range 11–20 years and found to be 0.25%. No correlation was reported between gender and VTE in the children with IBD (3). We found in our literature review that the development of CSVT was mostly detected in

the adolescent age group (75%) and the female to male ratio was different from the cohort studies.

At the same time, the time for the development of CSVT was approximately 10.5 months after the onset of the disease, which was similar to the reported values in the literature.

The clinical presentation of CSVT in the paediatric population is non-specific, most commonly including the triad of headache, emesis, and depressed mental status plus seizures (22). The limitations of our study were also similar to the literature.

The risk for thromboembolism increases in the normal population in IBD (3). The association between IBD and thrombosis is not yet completely clarified. Besides, some studies revealed that VTE was more frequently seen than Crohn's disease in the progression of UC (3, 20, 21, 23), while some studies showed that no significant difference was present (20, 24). Some studies consider VTE as a complication in the progression of UC, whereas some studies that accept VTE as a finding of the disease also exist (25). It had been reported that dehydration, accompanying infections, anaemia, concomitant autoimmune diseases, the presence of cyanotic heart disease, the comorbidity of nephrotic syndrome, corticosteroid treatment, the use of oral contraceptive, immobility, inherited thrombotic diseases, previous surgical operations, the activation of the disease, thrombocytosis, chromosomal disorders, and metabolic circumstances such as homocystinuria played role in the aetiology of CSVT which developed during the progression of UC in childhood (3, 22, 26–28). Its pathogenesis is associated with increased inflammatory response, genetic predisposition, loss of procoagulant factors through gastrointestinal system, temporary abnormalities in the clotting system, the increased levels of factor V and VIII beside decreased levels of protein S and antithrombin III during the disease's progression (5).

The main causes of thrombocytosis which is accepted as a risk factor in the development of CSVT in the patients with IBD are chronic inflammation, acute haemorrhage and the use of corticosteroid (26, 27). It has been stated that the essential factor in pathogenesis of thrombocytosis is the activation of thrombocytes due to the endothelial damage in the wall of the gastrointestinal system during the acute exacerbations. It had been confirmed that inflammatory mediators that increase during the endothelial damage also elevate the potential of VTE as well as activation of thrombocytes (26).

Conversely, the development of VTE in the absence of thrombocytosis in the subjects with IBD led to the conclusion that thrombocytosis does not cause exclusively thromboembolic phenomenon (26, 27). Another effective factor in the development of CSVT through the thrombocytes is use of corticosteroids in the treatment of UC. It has been suggested that these medicines inhibit the synthesis of prostacyclin by reducing the level of arachidonic acid in the vessel wall and create the predisposition to thrombosis by making the thromboxanes dominant (29).

On the other hand, corticosteroids have also inflammatory effects, reducing the effect on hypercoagulability and increasing the effect on the efficacy of heparin as well as the thrombogenic effect. Therefore, the effect of steroid treatment in thrombosis is controversial. It has also been shown in the evidence-based studies conducted in recent years (27, 30) that the use of corticosteroids does not increase the risk of thromboembolism in the patients with and without IBD (17, 27).

In our study, thrombocytosis was detected in 45.8% of the cases with UC and thrombocytosis was the unique detectable risk factor in only three cases (9, 10, 31).

Nonetheless, the development of thrombocytosis was present in 47% of the 17 cases who received corticosteroid treatment. The obtained data had shown that thrombocytosis could be rarely solely the risk factor for CSVT and that the use of corticosteroids does not lead to thrombocytosis.

It has been proposed that iron deficiency anaemia is another important factor in the aetiology of CSVT and stroke in the childhood age (32, 33). It has been observed that the presence of iron deficiency anaemia increases the risk for the development of vaso-occlusive stroke 3.8- to 10-fold in the childhood age group (33, 34). In recent years, available reports on this issue in the related childhood age group are in the form of case presentations (35–37). Despite this, the role of iron deficiency anaemia in the pathogenesis of CSVT is not yet certainly clarified (38). However, it has been emphasized that thrombocytosis accompanies 81% of the cases with severe anaemia and this accompanying thrombocytosis leads to CSVT (38). The risk for the development of thrombocytosis is 10.5-fold more in the children with iron deficiency anaemia than in the healthy children (34). On the other hand, iron is known as the negative feedback agent for the production of thrombocytes (35, 39). It has been emphasized that low serum iron level causes thrombocytosis by activating megakaryocytes with increased level of erythropoietin and that microcytosis which develops due to iron deficiency contributes to the formation of CSVT (35, 39, 40). It has been emphasized in a research on 65

cases with IBD and cerebral thrombosis that the presence of anaemia was detected in approximately half of the cases, while anaemia is the unique detectable risk factor in 31% of the cases (27). Stolz *et al* reported in a case-control study including 121 cases with iron deficiency that CSVT was significantly higher than in the control group in the cases with Hb level < 9 g/dL. In this study, thrombocytosis is not recognized as a significant risk factor in the development of CSVT, while the presence of severe anaemia (Hb < 9 g/dL) was reported as an important and an independent risk factor (RR 7.79, 95% CI 1.73, 35.10, $p < 0.008$) (38). In our study, the most common risk factors for CSVT in the patients with UC were anaemia (58.3%) and thrombocytosis (45.8%). Thrombocytosis and anaemia were the unique detectable risk factors for CSVT in three (12.5%) and two (8.3%) of the patients, respectively. The co-morbidity of anaemia and thrombocytosis was present in eight (33.3%) of the cases.

In the progression of IBD, the development of thrombosis usually occurs in the acute exacerbations (15, 26). It was detected in some studies that 71%–100% of cases with IBD accompanied by thromboembolism were in the active disease period (3, 7, 26, 27, 41). Some researchers have pointed out that the risk for the development of VTE increases 2-3-fold in the patients with active IBD than in the ones with IBD in the inactive period and that this risk increases during the passage from moderate exacerbation to severe exacerbation (3). It was also reported that time duration is an important factor in the development of thrombosis as well as disease activity. It has been reported that the cases with medical history of IBD longer than 2 years generally carry higher risk of thromboembolism than the other cases (3). The development of CSVT in the active stage of the disease is associated with the increased levels of fibrinogen, prothrombin fragment F1+2, thrombocytes, plasminogen activator inhibitor-1, and soluble thrombomodulin (15). It has been reported that immobility and fluid loss also contribute in addition to excessive clotting developing due to disease activity (15). In our study, 95.8% of the cases with UC accompanied with CSVT were found in the active exacerbation stage. The median value of the time for the development of CSVT was 10.5 months.

Another risk factor for thrombosis in the patients with UC was inherited thrombophilic disorders (26). In the childhood age, inherited thrombophilic disorders were confirmed as the risk factors in 36%, 44% and 33% of the cases with VTE, ischaemic stroke and IBD accompanied with VTE, respectively (3). The most common inherited risk factors for thromboembolism in IBD patients were factor V Leiden mutation, G20220A mutation in the prothrombin gene and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene (42). The most frequently investigated factor among these disorders in recent years was factor V Leiden mutation. Jackson *et al* reported the incidence of factor V Leiden mutation as 5% in their study on 52 cases who had IBD and thromboembolism (43). The risk of thrombosis increased approximately fivefold in the IBD patients with heterozygous for factor V Leiden mutation and G20220A mutation in the prothrombin gene (27). Some authors who do not accept these inherited thrombophilic disorders in IBD patients as a risk factor besides the main risk caused by the main disease since the report showing the relationship between IBD and thrombophilia are mainly published as a case report (15, 26). They suggested that this issue has to be studied by multicentres, including a larger number of IBD patients with thrombosis, to clarify the relationship between IBD and inherited thrombophilic disorders (42). In this review, 41.6% of the cases with UC had inherited thrombophilic disorders.

It is an undeniable reality that the risk for venous thrombosis increases in UC. Therefore, it is recommended to apply prophylactic treatment in recent years to reduce risk for thrombosis in the presence of additional risk factors such as immobility, thrombophilia, thrombocytosis (> 750 000/mm^3) and severe disease (Pediatric Ulcerative Colitis Activity Index > 45) that accompany UC in the childhood age (3). Also the recommendations for dipyridamole therapy as outpatient are available for the selected patients and the ones who have these additional risk factors (3, 7). Prophylactic oral and IV iron therapy are involved in the other preventive recommendations for iron deficiency anaemia that plays a role in the aetiology of CSVT.

Oral iron preparations are available for the patients with IBD in whom intravenous iron preparations are contraindicated (27). However, a consensus on iron prophylaxis has not been established.

There is a consensus between the guides on administering anticoagulants in the acute therapy of CSVT except neonates (44–46). The most important effect of the anticoagulants used in the treatment of CSVT is the prevention of newly developing venous infarction. The greatest conflict of the anticoagulant treatment is causing potential intracranial haemorrhage although it leads to the improvement of pulmonary embolism and neurological findings (27).

In the presence of acute ischaemic stroke which developed after CSVT, ultra-fractionated heparin (UFH) and LMWH treatment were recommended as the initial therapy after the elimination of cardioembolism and craniocervical dissection by the American Heart Association (AHA) (46) and the American College of Chest Physicians (ACCP) (44). However, this protocol is different from the guide by the United Kingdom Royal College of Physicians (44) that they recommend to initiate therapy by using only aspirin. Among the recommended acute treatment principles for CSVT are that the UK guide recommends to administer anticoagulant therapy until recanalization (44). According to the Chest guidelines, UFH and LMWH were recommended to initiate and administer treatment for LMWH or warfarin for 3–6 months during the follow-up period. This guide recommends thrombectomy or surgical decompression for the resistant cases, while thrombolysis is suggested for the selected cases. It is stated that anticoagulant therapy should not be administered in the presence of bleeding and that it can be tested if the progression of thrombosis is detected by the repeated imaging methods (44). The AHA 2008 Protocol suggests UFH or LMWH as the initial therapy, while it gives the treatment of only warfarin for 3–6 months which is different from Chest ACCP Guidelines. The same initial therapy is recommended in the presence of CSVT accompanied with intracranial haemorrhage. The treatment of local thrombosis is suggested in the irresponsive cases to therapy (46). The more commonly preferred treatment protocol in our study was to initiate patients with UFH and LMWH and to continue with warfarin and LMWH. Except these, the rate of the patients who received only LMWH was 25%, whereas rate of the patients who received only aspirin was 8.3%. No treatment was given because of the risk for bleeding in only two patients.

Paediatric stroke due to CSVT, being the 10th leading factor in paediatric deaths, has a mortality rate of 10% (22, 47, 48). The mortality rate in the presence of CSVT accompanying IBD was reported in 5.7% of the cases (3). The relapse rate for CSVT in the childhood age was < 5%, while this rate ranged between 15% and 20% in haemorrhagic stroke and arterial ischaemic stroke (22, 47, 48). A permanent neurological deficit developed in three-fourth of the surviving child cases with CSVT (22). The partial recovery rate in the cases with CSVT in the presence of IBD was 34%. Early and late recurrences were observed in 11% and 10% of these cases, respectively (3). The reported recovery rate without a sequela in the cases with CSVT in the presence of UC was 79.2%. The mortality rate was found in 8.3% of the cases, as in the literature. The partial recovery rate was detected in 12.5% of the cases.

In conclusion, IBD was a risk factor for venous thrombosis. The risk for thromboembolism was higher than the normal population because of the predisposition to hypercoagulation in the active period in the patients with IBD. The prevention of the facilitating factors such as infections during the acute periods of the disease, dehydration, the accompanying presence of anaemia and thrombocytosis is essential. Venous thrombosis should be considered in differential diagnoses when symptoms and findings such as headache, cranial nerve involvement, papilloedema and loss of motor function accompany the course of UC.

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